Bioengineering of the Blood-Brain Barrier Permeability

Grant R01NS50660 | Period of support: 7/2005 – 6/2009

Challenge/Problem: Effective drug therapy of the brain-related diseases often depends on drug transport from blood to the brain across the blood-brain barrier (BBB). A family of ABC drug efflux transporters expressed on brain capillary endothelial cells is primarily responsible for drug permeability of the BBB. Specific knockdown of these proteins may enhance brain chemotherapies.

Progress: An inhibitory RNA-producing plasmid was selected that knocked down the MRP4 gene in vitro. This transporter was found responsible for efflux of nucleoside analogs – drugs efficient in therapy of HIV and brain tumors. Nanogels with enhanced ability to the cellular internalization were identified as carriers for plasmid delivery and brain-targeting by peptides.

Approach: RNA interference will be used for inhibition of selected drug efflux transporters. Our brain-targeted RNA Interference-Producing system consists of three major components: (i) RNA-producing plasmid/or small Interfering RNA, (ii) Nanogel particles delivering these nucleic acids in the blood, and (iii) Brain-homing vector peptide attached to the Nanogel surface. Transfection of the BBB may result in transient inhibition of a related gene and emergence of a “window” for drug treatment.

Current/Near Term Products: Nanogel carriers for encapsulation of plasmid DNA or small interfering RNA modified by brain-specific homing peptides. Advanced Nanogels with biodegradable backbone and reduced cytotoxicity may be considered as near term products.

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Future Plans: (1) Optimization of the transfection by Nanogel carriers using backbone engineering, (2) Transfection enhancement in primary brain capillary endothelial cells by specific peptide targeting, (3) Evaluation of selected Nanogel-based transfection systems in animal models using fluorescent imaging. (4) “Proof of the concept” using radioactive drug for demonstration of drug delivery in brain of animals.

Keywords: blood-brain barrier, drug permeability, RNA interference, Nanogel, brain-homing peptide